Central Nervous System Involvement at Diagnosis in a Case of Pediatric CD30+ Anaplastic Large Cell Lymphoma

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Central nervous system (CNS) involvement in Ki-1/CD30 lymphoma is extremely rare, in contrast to the frequent involvement in other types of pediatric non-Hodgkin's lymphoma. No mechanism has yet been proposed to explain the sparing of the blood brain barrier in Ki-1/ lymphoma. We present a 2-year-old boy who was admitted to the Department of Pediatric Hemato-Oncology due to lethargy, progressive breathing difficulties, massive diffuse lymphadenopathy, hepatosplenomegaly, and ichthyosis-like skin involvement with epidermolysis. A lymph node biopsy was compatible with Ki-1/ CD30 anaplastic large cell lymphoma (ALCL). Bone marrow aspirate and biopsy demonstrated reactive hyperplasia. Cytogenetic analysis displayed hyperdiploid cells with 1p(−) in most cells. Cerebrospinal fluid examination showed pleocytosis with CD30+ cells. Possible mechanisms which could enable CNS involvement in this unusual case are discussed. **Med. Pediatr. Oncol. 28:132–135** © 1997 Wiley-Liss, Inc.

Key words: childhood malignancies; non-Hodgkin's lymphoma; Ki-1/CD30 positive lymphoma

INTRODUCTION

Childhood non-Hodgkin's lymphomas (NHL) are nearly all high-grade aggressive tumors of one of three histologic types: lymphoblastic, small noncleaved cell, or large cell (LCL) [1]. LCLs constitute 20–25% of childhood NHLs and are cytologically, immunologically, and clinically heterogenous. In 1982, a new monoclonal antibody was described, Ki-1, detecting a 120 kd protein, expressed in normal activated lymphocytes, and on reactive Reed-Sternberg cells [2]. The subsequent generation of at least eight other monoclonal antibodies reacting with this protein enabled the creation of the CD30 cluster [3].

Extensive immunohistologic studies with the Ki-1 monoclonal antibody led to the identification of a group of LCLs characterized by subtotal effacement of the lymph node architecture, paracortical growth pattern, spread to the sinuses, polymorphic appearance, and expression of the CD30 antigen by virtually all neoplastic cells [4,5]. This has recently been included in the updated Kiel classification as a high-grade anaplastic large cell lymphoma (ALCL), Ki-1/CD30+ [6], and in the revised European American lymphoma classification [7].

Ki-1/CD30+ ALCL constitute roughly 30–40% of all pediatric LCLs [8]. Ki-1/CD30+ ALCL is associated with peripheral lymphadenopathy and frequent extranodal disease. Skin, bone, soft tissue, gastrointestinal tract, lung, and pleural lesions are quite common [8,9]. Bone marrow involvement is infrequent and is reported to be present in less than 10% of cases of Ki-1/CD30+ ALCL [10], and CNS involvement is extremely rare [11]. We describe a case of Ki-1+ ALCL that presented with generalized skin involvement, hepatosplenomegaly, generalized adenopathy, pulmonary infiltrates, and CNS involvement.

CASE REPORT

An Arab 2-year-old boy from the Gaza Strip was referred to our hospital because of lethargy, progressive dyspnea, massive diffuse lymphadenopathy and hepatosplenomegaly, and ichthyosis-like skin involvement with epidermolysis. A bone marrow aspiration showed reactive hyperplasia of all three lineages, without hemophagocytosis. A lymph node biopsy was compatible with Ki-1/CD30+ ALCL. Immunophenotyping of cell suspension preparation displayed two separate populations of cells, small and large, 50% of the large reactive with the CD30/ Ki-1. Both Ig gene and T-cell receptor were in germ line configuration. Cytogenetic analysis of 20 metaphases showed hyperdiploid cells with 1p-in most cells. Within

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Received 15 August 1995; accepted 22 January 1996.

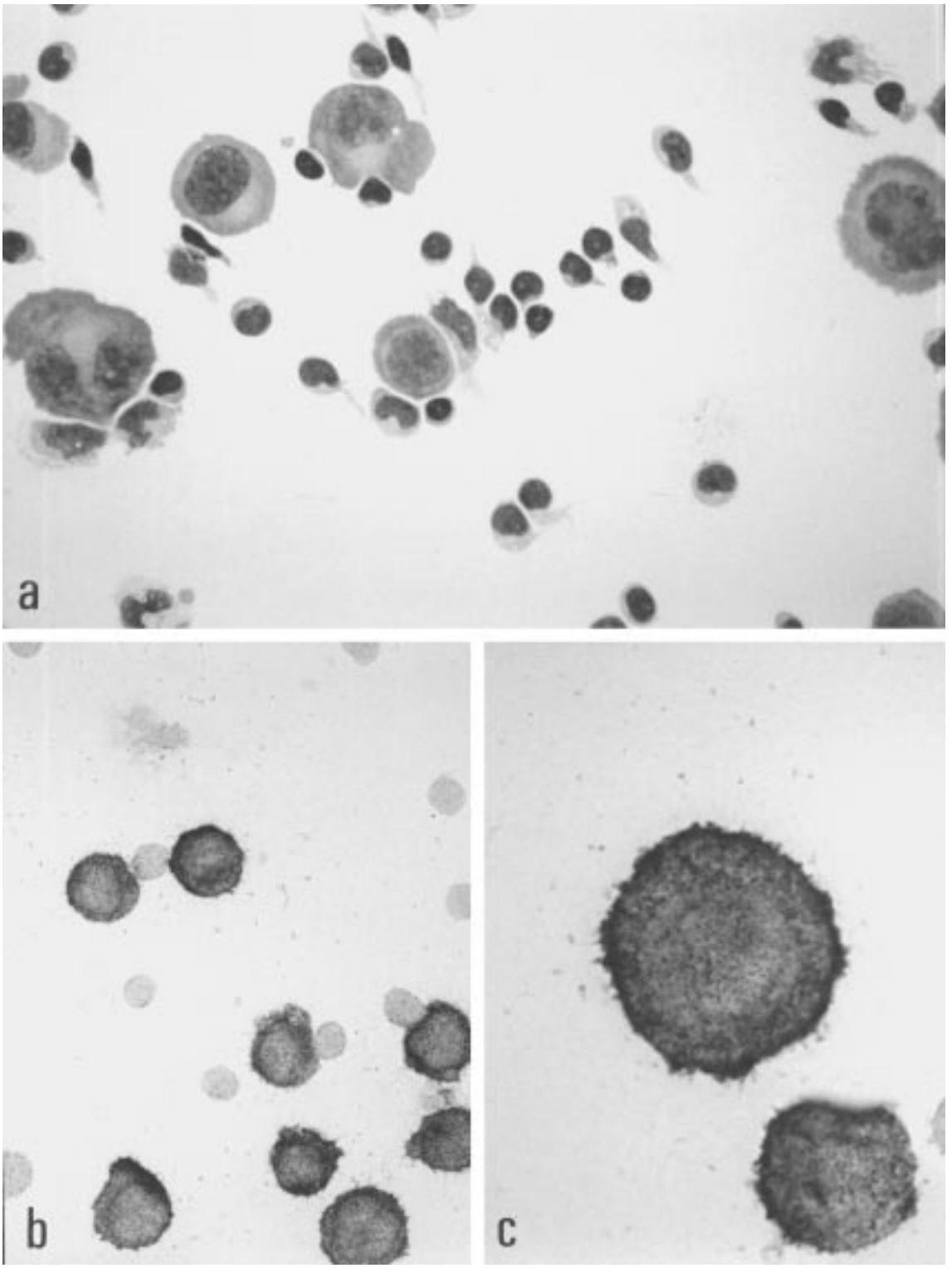

Fig. 1. **a:** Cerebrospinal cytospined cells displaying two populations of small and large lymphocytes. M-G, ×500. **b:** CD30/Ki-1+ lymphoblast. APAP, ×500. **c:** CD30/Ki+ large lymphoblast. APAP, ×1,250. Note unstained small lymphocyte.

3 weeks his situation deteriorated in spite of two courses of chemotherapy, antibiotics, and assisted ventilation. Cerebrospinal fluid (CSF) examination showed lymphocytic pleocytosis consistent with Ki-1/CD30+ (Fig. 1).

Bilateral pulmonary infiltrates and severe hypoxemia necessitated mechanical ventilation with high pressure and high oxygen concentrations. Few attempts to wean him from the assisted ventilation failed, and he subsequently died with respiratory insufficiency, bone marrow failure, and CNS involvement. Permission for autopsy was denied.

DISCUSSION

This patient demonstrates the clinical spectrum of an aggressive Ki-1/CD30+ childhood lymphoma, initially presenting with generalized skin involvement, liver function impairment, suppressed immunity, and surprisingly a terminal CNS involvement with CSF pleocytosis. In a recent review of seven series of pediatric Ki-1 ALCL, in 266 cases there were rare cases of bone marrow involvement and no initial CNS involvement reported [1]. Only one patient with stage II T-ALCL with cutaneous primary involvement relapsed 4 months following diagnosis, in the CNS [11].

Why is CNS involvement in Ki-1 ALCL so rare compared to the 15–20% CNS involvement in pediatric NHL as a whole? The CD30 molecule and its ligand (CD30L) are newly recognized members of the TNF receptor and TNF ligand superfamilies, respectively. The biological role of CD30/CD30L interaction is still largely unknown. It had been shown that the CD30+ molecule or the CD30/CD30L system has a regulatory effect on proliferation, differentiation, and apoptosis [12,13]. The presence of soluble CD30 molecules has been shown in the supernatants of CD30-expressing lymphoma cells [14]. It would not be surprising if the soluble CD30 molecule would exert its effect on the blood brain barrier, in the same manner that it alters ionic flux through T-cell receptor positive Jurkat T cells.

The nonrandom translocation t(2:5) (p23:q35) creates a fusion product NPM/ALK protein (p80) [15,16]. One may speculate that the protein exerts its effect in an unknown fashion on the brain. ALK, with its protein kinase activity, is expressed in normal brain, but the fusion to nucleophosmin may down regulate its expression and subsequently its action on the brain.

The role of apoptosis in the control of CNS involvement is quite interesting. It has already been shown that the CD30L may induce cytolytic cell death of most CD30+ ALCL lines. Is it possible that CD30 preferentially initiates apoptosis in the leptomeninges, preventing the tumor cell from entering the blood brain barrier or surviving there [17]. Control of apoptosis by cell surface receptors molecules such as TNF-R, apo-1 (FAS), and NGF-R is well known [17]. In some systems, binding of the specific ligand initiates the apoptosis pathways. In other systems, deprivation of viability factors results in a programmed cell death. The lack of growth factors in the CSF may explain the preferential death of the penetrating cells.

The traffic of lymphocytes in the various compartments of the immune system was reported in recent years as being regulated by the concerted expression of cell surface adhesion molecules such as selectin, PSGL1, MAC-1, LFA-1, VLA-4, ICAM-1, ICAM-2, and VCAM-1 that mediate tissue and organ-specific homing [18]. ALCL cells may lack the molecules which enable their penetrating and homing capacities to the CNS through the blood brain barrier.

This very unusual case demonstrates an exception to the unique clinical characteristic of Ki-1/CD30 cells, in which no CNS involvement is found. It seems that in this unfortunate patient, a secondary genetic molecular change resulted in a subpopulation of lymphoma cells with a penetrating capacity across the blood brain barrier.

ACKNOWLEDGMENTS

This work was supported in part by the Ministry of Absorption of Israel.

REFERENCES

1. Murphy SB: Pediatric lymphomas: Recent advances and commentary on Ki-1 positive anaplastic large cell lymphomas of childhood. Ann Oncol 5 (Suppl 1):531–533, 1994.
2. Schwab U, Stein H, Gerdes J, et al.: Production of a monoclonal antibody specific for Hodgkin and Sterenberg-Reed cells of Hodgkin's disease and a subset of normal lymphoid cells. Nature 299:65–69, 1982.
3. Schwarting R, Stein H: Cluster report: CD 30. In Knapp W, Droken B, Bilks WR, Rieber EP, Schmidt RE, Stein H, Von dem Borne (eds): "Lymphocyte Typing IV." Oxford: Oxford University, 1989, p. 419.
4. Kadin ME: Ki-1 positive anaplastic large-cell lymphoma: A clinico-pathologic entity? J Clin Oncol 9:533–536, 1991.
5. Stein H, Dallenbach F: Diffuse large cell lymphomas of B and T-cell type. In Knowles DM (ed): "Neoplastic Hematopathology." Baltimore: Williams & Wilkins, 1992, p. 675.
6. Stansfell AS, Diebold J, Kapanci Y, Kellnyi G, Lennert K, Mioduszewka O, Noel H, Rilke F, Sandstrom C, Van Unnik JAM, Wright DH: Updated kiel classification for lymphomas. Lancet 1:292, 1988.
7. Harris NL, Jaffe ES, Stein H, Banks PM, Chan JKC, Clean M, Delsol G, De Wolf-Peeters C, Falini B, Gatter KC, Grogan TM, Isaacson PC, Knowles DM, Mason DY, Muller-Hermelink H-K, Pileri S, Piris MA, Ralfkier E, Wranke RA: A revised European American classification of lymphoid neoplasms: A proposal from the international lymphoma study group. Blood 84:1361, 1994.
8. Sandlund JT, Pui CH, Santana VM, Mahmoud A, Roberts WM, Morris S, Raimondi S, Ribeiro R, Crist WM, Lin JS, Mao L, Berard CW, Hutchinson RE: Clinical features and treatment outcome for children with CD30(+) large cell non-Hodgkin's lymphoma. J Clin Oncol 12:895–898, 1994.
9. Reiter A, Schrappe M, Tiemann M, et al.: Successful treatment strategy for ki-1 anaplastic large cell lymphoma of childhood: A prospective analysis of 62 patients enrolled in three consecutive

Berlin-Frankfurt-Munster group studies. J Clin Oncol 12:899–908, 1994.
10. Greer J, Kinney MC, Collins RD, et al.: Clinical features of 31 patients with Ki-1 anaplastic large cell lymphoma. J Clin Oncol 9:539–547, 1991.
11. Brugieres L, Patte C, Pacquement H, et al.: Large cell anaplastic lymphoma in children: Therapeutic results in 75 patients treated with 3 consecutive polychemotherapy regimens. Fifth International Conference on Malignant Lymphoma, Lugano, June 1993 (Abstract 253).
12. Gruss HK, Boiani N, Williams DE, et al.: Pleiotropic effects of the CD30 ligand on CD30 expressing cells and lymphoma cell lines. Blood 83:2045, 1994.
13. Falini B, Pileri S, Pizzolo G, Durkop H, Flenghi L, Stirpe F, Martelli MF, Stein H: CD30 (Ki-1) molecule: A new cytokine receptor of the tumor necrosis factor receptor superfamily as a tool for diagnosis and immunotherapy. Blood 85:1–14, 1995.
14. Josimovic-Alasevic O, Durkop H, Schwarting R, et al.: Ki-1(CD30) antigen is released by Ki-1 positive tumor cells in vitro and in vivo-I partial characterization of soluble Ki-1 antigen and detection in cell culture supernatants and in serum by an ELISA. Eur J Immunol 19:157, 1989.
15. Fischer P, Nachera E, Mason DY: A Ki-1 (CD30) positive human cell line (Karpas 299) established from a high grade-non-Hodgkin's lymphoma, showing a 2:5 translocation and rearrangement of the T-cell receptor beta-chain gene. Blood 72:234–240, 1988.
16. Morris SW, Kirstein MN, Valentine MB, et al.: Fusion of a kinase gene, ALK, to a nuclear protein gene, NPM, in non-Hodgkin's lymphoma. Science 263:1281–1284, 1994.
17. Nagata S, Golstein P: The FAS death factor. Science 267:1449–1456, 1995.
18. Springer TA: Traffic signals for lymphocyte recirculation and leukocyte emigration: The multistep paradigm. Cell 76:301–314, 1994.